

## Human trophoblast progenitors: where do they reside?

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### Public Summary:

In humans, very little is known about the factors that regulate trophoblast (TB) specification, expansion of the initial TB population, and formation of the cytotrophoblast (CTB) populations that populate the chorionic villi. The absence of human trophoblast progenitor cell (hTPC) lines that can be propagated in vitro has been a limiting factor. Because attempts to derive TB stem cells from the trophectoderm of the human blastocyst have so far failed, investigators use alternative systems as cell culture models including TBs derived from human embryonic stem cells (hESCs), immortalized CTBs, and cell lines established from TB tumors. Additionally, the characteristics of mature TBs have been extensively studied using primary cultures of CTBs and explants of placental chorionic villi. However, none of these models can be used to study TB progenitor self-renewal and differentiation. Furthermore, the propagation of human TB progenitors from villous CTBs (vCTBs) has not been achieved. The downregulation of key markers of cell cycle progression in vCTBs by the end of the first trimester of pregnancy may indicate that these cells are not a source of human TB progenitors later in pregnancy. In contrast, mesenchymal cells of the villi and chorion continue to proliferate until the end of pregnancy. We recently reported isolation of continuously self-renewing hTPCs from chorionic mesenchyme and showed that they differentiated into the mature TB cell types of the villi, evidence that they can function as TB progenitors. This new cell culture model enables a molecular analysis of the seminal steps in human TB differentiation that have yet to be studied in humans. In turn, this information can be used to trace the origins of pregnancy complications that are associated with faulty TB growth and differentiation.

### Scientific Abstract:

In humans, very little is known about the factors that regulate trophoblast (TB) specification, expansion of the initial TB population, and formation of the cytotrophoblast (CTB) populations that populate the chorionic villi. The absence of human trophoblast progenitor cell (hTPC) lines that can be propagated in vitro has been a limiting factor. Because attempts to derive TB stem cells from the trophectoderm of the human blastocyst have so far failed, investigators use alternative systems as cell culture models including TBs derived from human embryonic stem cells (hESCs), immortalized CTBs, and cell lines established from TB tumors. Additionally, the characteristics of mature TBs have been extensively studied using primary cultures of CTBs and explants of placental chorionic villi. However, none of these models can be used to study TB progenitor self-renewal and differentiation. Furthermore, the propagation of human TB progenitors from villous CTBs (vCTBs) has not been achieved. The downregulation of key markers of cell cycle progression in vCTBs by the end of the first trimester of pregnancy may indicate that these cells are not a source of human TB progenitors later in pregnancy. In contrast, mesenchymal cells of the villi and chorion continue to proliferate until the end of pregnancy. We recently reported isolation of continuously self-renewing hTPCs from chorionic mesenchyme and showed that they differentiated into the mature TB cell types of the villi, evidence that they can function as TB progenitors. This new cell culture model enables a molecular analysis of the seminal steps in human TB differentiation that have yet to be studied in humans. In turn, this information can be used to trace the origins of pregnancy complications that are associated with faulty TB growth and differentiation.